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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004412

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Precautionary Labeling for Hartz Rabon Dog Collar

TO: Mr. George LaRocca, PM 15
Registration Division (TS-767)

FROM: Byron T. Backus *Byron T. Backus*
Toxicologist *4-16-85*
Toxicology Branch

THROUGH: Clint Skinner, Ph.D. *Clint Skinner 4-16-85*
Head, Section III
and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Product: Rabon Dog Collar

Registration: 2596-62

Registrant: Hartz Mountain Corp.

Tox. Chem. 217A

Action Requested:

The Registration Division has requested a Toxicology response to this registrant's reply to a previous Toxicology review. The registrant's reply includes an addendum to a previously submitted (and reviewed) study.

Background:

This is the third review (previous reviews were dated 3/13/84 and 08/29/84) relating to the adequacy of current precautionary labeling for this product.

The initial review of 3/13/84 noted that an incident has been reported in which a collar was placed on a pregnant cocker spaniel bitch, who subsequently had five puppies, two of which died 2 days after birth with symptoms similar to cholinesterase inhibition. The incident was reviewed at FDA, and their comment was that the labeling seems deficient in warnings concerning neonatal exposure.

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The registrant has maintained that current precautionary labeling is adequate, and has submitted a number of studies. The initial review (3/13/84) examined 5 studies (plus two one page summaries which were more in the nature of testimonials than actual toxicological data), of which four studies were classified as core supplementary data and one was classified as invalid.

Among the studies which were examined in the initial review was one titled: "Effect of the 10% Stirofos Flea Collar on Reproductive Capacity of the Bitch Dog." While the study had a number of failings, it suggested the possibility that bitches wearing a collar with the active ingredient had pups which averaged less weight at 4 weeks of age than those of bitches wearing a placebo collar. According to the review of 3/13/84:

"...All 4 control bitches which raised 6 or more surviving pups had litters averaging at least 0.98 kg/pup at 4 weeks, while of 7 test litters with 6 or more surviving pups four averaged less than 0.95 kg/pup at 4 weeks. One test group litter with 6 surviving pups averaged 0.77 kg/pup. Another test group with only 5 pups averaged 0.86 kg/pup at 4 weeks. There were no significant differences in average birth weights between placebo and test collar groups."

The material covered in the review of 8/29/84 included a report titled "Effects of the Use of an SD-8447 Collar on Puppies."

Comments and Conclusions:

1. With the additional information (including identification of the collar, sexes of individual animals, which were medicated, total number of animals in each litter) received 11/19/84 the study titled "Effects of the Use of An SD-8447 Collar on Puppies" has been reclassified as supplementary data.
2. Despite this reclassification, the study cannot be used to demonstrate any margin of safety in exposure to newborn puppies. As was indicated in the review of 08/29/84 this study, even with additional data, could not be considered relevant to the question of toxicity of newborn puppies as the animals were already 4 weeks old when the collars were placed on them. The only study that the Agency has on hand involving newborn puppies is the one which was reviewed 3/13/84.

3. In response to the statements made in the registrant's letter of November 16, 1984 that a protocol for the White Eagle study was submitted to the Agency with a letter on the 18th of November 1983, and that "We would have anticipated some comment from EPA if cholinesterase measurements were considered to be necessary" it is noted that at that point the study was already underway, as an interim report (dated November 15, 1983) was also submitted. There is no record that the protocol had been submitted to the Agency for comment before the study was initiated. By the time the material received in November of 1983 had been reviewed (3/13/84), the White Eagle study was finished (the last blood chemistry was done 12/21/83).

The review of 3/13/84 did have the following comment in the conclusions section with respect to the interim White Eagle report:

"It is not anticipated that this study, even when completed, will provided significant data. Maximum exposure is to a single collar. No cholinesterase measurements are being made..."

Rabon is a demonstrated cholinesterase inhibitor in mammalian species, and its toxicity is primarily (but not necessarily exclusively) due to this activity. While a number of blood chemistry parameters were examined in the White Eagle study, cholinesterase activities, which - provided a sufficient number of animals had been used for statistical purposes - would have been the most appropriate and sensitive indicator for exposure to Rabon, were not measured.

4. The response that the lower body weight of the puppies exposed to the test collar was a result of their having been mostly derived from larger litters relative to the controls is considered as additional evidence of the poor design of this study.
5. It is not surprising that the pups used in the study were "...in the upper half of all pups for the three ages at which weights were taken" as they were derived from litters of 4 or 5 puppies, and the normal litter size for a beagle is about 7.
6. In response to the statement that "an overwhelming body of information is available and has been submitted to the Agency previously demonstrating that this collar does not inhibit cholinesterase" the review of 3/13/84 found a number of deficiencies the studies received in November, 1983, and they must be regarded as inconclusive. Copies of the data evaluations which were a part of the review of 3/13/84 should be made available to the registrant.

7. In summary, the position of the Toxicology Branch remains unchanged. Labeling for this product should be revised to state that pregnant bitches and newborn and nursing puppies should not be exposed to this collar. It would also be appropriate to state that additional cholinesterase inhibiting compounds should not be used on dogs wearing this collar.

Discussion:

The data received 11-19-84 include 1) weights of the individual puppies used in the study (6 controls, 12 animals wearing the test collar) at 29 and 90 days after study initiation; 2) analysis of the test collar (which contained 14.5% Rabon); and 3) individual analytical results for the various blood chemistry parameters (glucose, blood urea nitrogen, creatinine, BUN/creatinine ratio, sodium, potassium, chloride, carbon dioxide, anion gap, alkaline phosphatase, calcium, phosphate, prothrombin, albumin (called "aluminum" in the report), globulin, cholesterol, triglycerides, total bilirubin, uric acid, aspartate amino transferase (SGOT), alanine amino transferase (SGPT), creatinine phosphokinase, and lactate dehydrogenase).

There were no noticeable effects on any of these parameters. However, the technical material is a cholinesterase inhibitor, and the most sensitive indicator of an effect related to exposure would have involved cholinesterase activity measurements, which were not reported. Additionally, exposure was only at "use level," and puppies were already 4 weeks old at the start of the study. The question of toxicological effects on newborn puppies remains unresolved.

None of the toxicological studies which have been received from the registrant have involved exposures at greater than those associated with "normal use." Without such information it is not possible to come to any conclusions regarding what sort of safety margin exists between the use of this collar and that level of exposure at which effects can occur in dogs. Considering genetic variability in dogs, and also such factors as age and general physical condition, some dogs are going to be more susceptible than others to possible adverse effects. The smaller the safety margin (here undefined), the greater the possibility of adverse effects.

Data Evaluation Report:

D'Ver, A.S. V.M.D. Effects of the Use of an SD-8447 Collar on Puppies Addendum to Final Report White Eagle Study #137. Dated November 14, 1984. Received at EPA 11-19-84; in Acc. 255701.

Data Evaluation Report

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Compound:

Rabon

Study type:

Collar exposure (dermal) - dog

Citation:

D'yer, A.S. V.M.D. Effects of the Use of an SD-8447 Collar on Puppies Hartz Protocol #83-1. White Eagle Study No. 137, dated July 3, 1984, with an addendum (by the same author) titled: Effects of the Use of an SD-8447 Collar on Puppies Addendum to Final Report White Eagle Study #137. The addendum is dated November 14, 1984. Received at EPA 11-19-84; in Acc. 255701.

Reviewed by:

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Approved by:

Clint Skinner, Ph.D.
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Review Section III
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Core Classification:

Supplementary

Conclusions:

1. The study indicates that, among puppies which wore a single 14.5% Rabon collar from the age of 1 to 4 months, there were no changes out of the ordinary (or which were related to collar exposure) for a number of blood chemistry parameters. However, the blood chemistry parameters which were measured did not include plasma and/or RBC cholinesterase activities.
2. As control puppies tended to originate from litters that were slightly smaller than those of puppies wearing an active-ingredient collar, and as the total number of puppies was not sufficiently large enough for statistical purposes, no definite conclusions can be made regarding whether or not exposure to this collar in young puppies may be associated with a reduced weight gain.
3. It has been noted that the three males in group 2622 (wearing the test collar) which were part of a total litter of 4 averaged 6.33 kgs on 12/21/83, while the three male controls of group 2446 (also part of a

total litter of 4) averaged 6.92 kg. However, 2 males of the 2622 group had been treated with Chloramphenicol, which indicates they had had respiratory disease. This is another example of the inherent variability in this study, although with the small numbers of puppies involved the weight difference would not be statistically significant even if the Rabon-exposed animals had not been sick.

Materials:

Eighteen beagle puppies, four weeks of age when exposure was initiated, from 6 litters. Three puppies from each of 2 litters (#2446, #2294) were designated as controls, while three puppies from each of the other 4 litters (#2529, #2797, #2666, #2622) were exposed to the SD-8447 (Rabon) collar.

SD-8447 collars; containing 14.5% Rabon.

Placebo collars.

Procedure:

Three puppies in each of 2 litters (each with a total of 4 puppies) were fitted with placebo collars. Three puppies in each of 4 other litters (3 litters contained five pups, and 1 contained 4 pups) were fitted with SD-8447 collars. All other puppies in these 6 litters, although not used for study purposes, were fitted with placebo collars.

Blood was taken from each puppy on 9-22-83, 10-21-83 and 12-21-83, at which time each was also weighed and given a complete physical examination.

Values for the following blood chemistry parameters were obtained by use of a Technicon Sequential Multiple Analyzer:

GLUH.	AGAP = (C1+CO ₂)-(Na)	PRO (prothrombin)
BUN	AP	ALB (albumin)
CREA	Ca	GLOB
BUN/CREA RATIO	PO ₄	CHOL
NA	SGOT	TRIG
K	SGPT	TBIL (total bilirubin)
C1	LDH	Uric acid
CO ₂	CPK (creatine phosphokinase)	

According to the letter of November 16, 1984 "Statistics were not employed for the blood test measurements since values were in the normal range. They were employed for comparison of group weights..."

Results:

One control pup and one exposed pup died, as did a non-study littermate of the exposed pup that died. They were diagnosed as having pneumonia. Several other puppies were treated with Chloramphenicol for respiratory disease. Of the 5 surviving controls, 2 had been treated with Chloramphenicol. Of the 11 surviving exposed puppies, 3 had been treated with Chloramphenicol, and 3 had been treated with Neomycin sulfate.

No irritation or other signs attributable to the collars were observed. At the conclusion of the study "all pups appeared to be healthy."

Phosphate levels were measured for only 4 of the exposed puppies (and none of the controls) at 3 months.

Triglyceride level was the only blood chemistry parameter that even had the appearance that it might have been noticeably affected by exposure to the collar. From the averages as originally presented:

AVERAGE, BLOOD CHEMISTRY VALUES FOR TRIGLYCERIDE LEVELS

	9/22/83	10/21/83	12/21/83
Controls	74.2	39	24.2
Exposed	56.5	22.6	7.2

However, after examining the individual data, it is the conclusion of this reviewer that there was probably no actual effect on this parameter (exposed puppies consistently averaged about 17 units below controls, and this parameter was somewhat variable at the individual level). There is also a question of the significance of this finding, particularly with all other indicators of liver function in normal ranges.

The following paragraph is from the review of August 29, 1984:

The average initial weight for the five controls which survived was 1.15 kg; for the 11 surviving exposed puppies it was 1.16 kg. Three months later averages were 6.7 and 6.25 kg respectively. However, the control average was depressed by one animal which weighed only 4.75 kg; all other controls weighed 6.5 to 8 kg. Among the exposed animals 36% (4 out of 11) weighed less than 6 kg. The low-weight control animal was a littermate of the control which had died.

The registrant has now submitted information indicating that both control litters had only 4 puppies, but that 3 of the 4 exposed litters had 5 puppies. "All pups under 6.0 kg were from litters of 5 each."

Only one of the exposed groups (consisting of 3 males) was derived from a litter of 4 puppies. The average weight for these 3 puppies at 3 months was 6.33 kg; for the 3 control males of the 2446 group it was 6.92 kg. However, two of the exposed puppies had been treated with Chloramphenicol, indicating they had probably had respiratory problems. Also, the relatively small numbers involved (3 puppies in each group, or a comparison of 1 litter vs. another litter) indicates that there is probably no statistically significant difference between these average weights.

Discussion:

Cholinesterase data are completely lacking. The information, as provided, simply indicates that the other blood chemistry parameters

were within normal ranges at 1 and 3 months following exposure.

No conclusions can be made as to whether or not the reduced weight gains in puppies wearing the Rabon collar were due to exposure to this active. There are too many variables associated with the weight data, and the numbers of puppies and/or litters in this study were too low for a valid statistical comparison.

In summary, this study is extremely limited insofar as providing useful (or significant) data to demonstrate product safety.